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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,749	01/14/2002	Michael Vajdy	16464.003	5494

7590 07/12/2011

CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
07/12/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/051,749	VAJDY ET AL.
	Examiner	Art Unit
	BENJAMIN P. BLUMEL	1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-10,19-28 and 35-42* is/are pending in the application.

4a) Of the above claim(s) *6, 7,22-28 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,8-10,13-15,19-21,29,30,35-39,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/22/2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Examination of the instant application will be conducted by Examiner Blumel.

Applicants are informed that the rejections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's arguments and/or amendments.

Election/Restrictions

This application contains claims 6, 7, 22-28 and 40 are drawn to inventions and species nonelected with traverse in the reply filed on 4/5/04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1, 5, 8-10, 19-21, 35-39, 41 and 42 are examined on the merits.

Response to Arguments

Applicant's arguments filed 12/17/2010 have been fully considered but they are not persuasive. See responses below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(New Rejection Necessitated by Amendments) Claims 1, 5, 8-10, 19-21, 35-39 and 42 rejected under 35 U.S.C. 103(a) as being unpatentable over Malone et al. (US Pat. 6,110,898),

Olmsted et al. (US PGPub 20020141975), Barchfeld et al. (WO 98/42375) and Rappuoli et al. (WO 95/17211).

The claimed invention is drawn to a method of generating an immune response in a subject by administering intranasally during a multidose protocol, a composition comprising a detoxified bacterial ADP-ribosylating toxin and a replication-defective dendritic cell-tropic alphavirus vector. The toxin is a cholera toxin (e.g., PT-K9/G129), pertussis toxin (e.g., CT-S109) or an *E. coli* heat-labile toxin (e.g., LT-K63 or LT-R72). The vector comprises a polynucleotide encoding at least one antigen and the vector is a chimeric alphavirus particle containing a Venezuelan Equine Encephalitis (VEE) virus vector construct packaged with Sindbis (SIN) virus envelope glycoproteins. The "at least one antigen" is derived from a sexually transmitted pathogen, such as HIV-1. The immune response elicited is a HLA class I or II restricted response. The method also requires that nucleic acid molecules encoding a Class I MHC protein, Class II MHC protein, CD3, ICAM-1 or LFA-3.

As established in a previous office action, mailed 1/12/09, Malone et al. teach a method of inducing a mucosal immune response wherein an antigenic polynucleotide is administered to the vaginal, nasal or rectal mucosal membranes of a subject according to a multiple dose schedule. The polynucleotide can be part of a recombinant, chimeric viral vector [Abstract, lines 2-4; col. 3, lines 54-60; col. 14, lines 64-66; col. 15, lines 57-62; and col. 17, lines 14-17 and 61-63, in particular.] Malone et al. teach that the antigenic polynucleotide may be derived from a sexually transmitted virus such as HIV-1. [Col. 20, lines 7-10 and 23-25, in particular.] Malone et al. further teach that the polynucleotide be delivered by an alphaviral vector such as Sindbis or

Semliki Forest virus. [Col. 11, lines 39-41, in particular.] The alphavirus vector used by Malone et al. comprises a replicon. [Col. 2, line 66 to col. 3, line 1, in particular.] Malone et al. also disclose introducing a nucleic acid that encodes a Class I and/or a Class II MHC protein. [Col. 4, lines 60-65, in particular.] It should be noted that Malone et al. inherently discloses presenting an antigenic polynucleotide to dendritic cells. This is necessarily so because mucosal membranes are a natural environment for dendritic cells. Thus, by introducing an antigenic polynucleotide to a mucosal surface, Malone et al. necessarily discloses presenting the antigenic polynucleotide to dendritic cells. Additionally, as previously noted, Malone et al. inherently teaches eliciting an HLA class I or HLA class II response. This results because Malone et al. teaches administering the antigen-encoding polynucleotide to a human, which would necessarily cause an HLA class I and HLA class II response.

The difference between the claimed invention and the disclosure of Malone et al. is: while Malone et al. do not teach use of a chimeric alphavirus particle that contains a VEE viral vector construct packaged with SIN virus envelope glycoproteins, they do teach the use of a chimeric viral vector as part of the administered composition and the use of alphaviruses for delivering an antigen encoding gene of interest. Malone et al. do not teach the administration of a detoxified bacterial ADP- ribosylating toxin, which are adjuvants. However, it should be noted that Malone et al. do teach the use of adjuvants with their replication defective gene delivery vehicle. [Col. 3, line 61 to col. 4, line 3 and 36-47, in particular.] At the cited passage, Malone et al. suggest the use of detoxified bacterial ADP-ribosylating toxin as an adjuvant, including E, coil and cholera toxins.

While Malone et al. do suggest the use of an E.coli heat labile toxin as an adjuvant, Malone et al. do not teach the following toxins: LT-K63, LT-R72, CT-S109 and PT-K9/G129. However, the deficiency noted of Malone et al. is fully compensated by Barchfeld et al.

Barchfeld et al. teaches LT-K63, LT-R72, CT-S109, and PT-K9/G129. Barchfeld et al. teaches the use of these detoxified toxins as adjuvants. [Lines 15-20, page 5, in particular.] Barchfeld et al. discloses the adjuvants are mucosal adjuvants, as evidenced by Rappuoli, R. Rappuoli, R. teaches that the non-toxic mutants of the toxins are active as mucosal adjuvants.

Olmsted et al. teach the generation of chimeric alphavirus particles that contain the RNA replicon (viral vector) of one virus and the structural proteins of another alphavirus, such as VEE, Sindbis and Semliki Forest. Examples of the structural proteins are E2 and E3. [See paragraphs 217, 220 and 221] One specific example of the chimeric alphavirus is that of a Sindbis RNA replicon being combined with the structural proteins of VEE. [See paragraph 221] Olmsted et al. also teach that alphavirus-based replicon particles are effective at inducing mucosal immune responses [See paragraph 6] and that the alphaviruses replicons can encode antigens from HIV in order to provide an expression construct that can induce immune responses to HIV. [See paragraph 3]

Hence, at the time the invention was made, the use of LT-K63, LT-R72, CT-S109, and PT-K9/G129 as adjuvants are well known in the art. It would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made, to substitute the adjuvant of Malone et al. with the adjuvants of Barchfeld et al. (K63, LT-R72, CT-S109, and PT-K9/G129). Furthermore, based on the suggestion of Malone et al. to utilize chimeric viral vectors and the teachings of Olmsted et al. of generating chimeric alphaviruses with VEE and SIN, it would be

prima facie obvious to employ these chimeras in the induction of a mucosal immune response. At the time the invention was made, one of ordinary skill in the art would have been motivated to do so to enhance the immune response induced by the composition of Malone et al. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the substitution of equivalents, adjuvants, are routinely practiced in the art.

(New Rejection Necessitated by Amendments) Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Malone et al., Olmsted et al., Barchfeld et al. and Rappuoli et al. as applied to claims 1, 5, 8-10, 19-21, 35-39 and 42 above, and further in view of McCluskie and Davis (Journal of Immunology, 1998).

The claimed method also requires that the composition further comprise CpG.

As discussed above, neither Malone et al., Olmsted et al. or Barchfeld et al. teach the addition of a CpG oligonucleotide.

McCluskie and Davis teach that CpG oligonucleotides are a potent enhancer of systemic and mucosal immune responses. McCluskie and Davis also disclose that combined with another mucosal adjuvant, such as cholera toxin, the oligonucleotides and toxin act synergistically, giving stronger responses than those observed with 10 times more of either adjuvant alone. [See figures 2 and 3]

In addition to the summarized teachings above, one of ordinary skill in the art would have a reasonable expectation of success at adding CpG taught by McCluskie and Davis to the

composition being used in the claimed method since Malone et al. teach use of adjuvants with their compositions.

Response to arguments:

Applicant presents the following arguments in traversal of the rejection:

While Malone et al. teach the use of chimeric viral vectors as a vehicle for delivering the nucleic acid of interest; they do not teach the specific chimeric alphavirus particle that comprises a VEE vector construct and the structural proteins of SIN virus. Applicants also state that they surprisingly found that the claimed chimeric had a better immune response than the individual viruses themselves or when the opposite chimeric alphavirus particle was formed from VEE and Sindbis. Furthermore, nothing in the cited art (Malone et al., Barchfeld et al., Rappuoli et al. and McCluskie and Davis) would have led the skilled artisan to expect that administering a VEE virus vector construct packaged with SIN virus envelope glycoproteins would provide such an unexpectedly robust immune response.

Rebuttal:

In response, it is acknowledged that the previously cited references do not teach the use of a chimeric alphavirus particle in which a VEE viral vector construct is packaged with Sindbis structural proteins. However, Olmsted et al. teach the generation of chimeric alphaviruses that possess the RNA replicon (viral vector) of one type of alphavirus and the structural proteins (e.g., E2) of a different alphavirus. They also provide examples of these different alphaviruses, such as VEE, Sindbis or Semliki Forest. Therefore, based on the teachings of Malone et al. to employ a chimeric viral vector for inducing an immune response and the use of alphaviruses also

in the induction of immune responses, one of ordinary skill in the art would have a reasonable expectation of success at generating the chimeric alphavirus particles that contain VEE vectors packaged with structural proteins from Sindbis and administering said particles to a subject in order to induce an immune response. Furthermore, Gardner et al. (Journal of Virology, 2000) observed that E2 proteins of Sindbis virus variants are highly efficient at targeting and infecting immature human dendritic cells (DCs) and they established for the first time that alphavirus replicon particles can target human DCs. [See page 11850-left column] This improved targeting of DCs leads to increased lymphnode trafficking, co-stimulatory molecule secretion and MHC class I expression of the cells, thereby improve immune responses against any antigen present in the Sindbis capsid/virus. Therefore, the method arrived from the combined teachings of Malone et al., Olmsted et al., Barchfeld et al. and Rappuoli et al. would achieve the unexpected immune responses of figure 13 since the products that achieve this are taught by the above references combined. Therefore the claimed invention is rendered prima facie obvious.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BENJAMIN P BLUMEL/
Examiner
Art Unit 1648

/Zachariah Lucas/
Supervisory Patent Examiner, Art Unit 1648